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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,655	03/23/2004	Michael Sundstrom	31611-8A	2818

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EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,655	SUNDSTROM ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-21 and 26-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-21 and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/355,664.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *23 March 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 11-21 and 26-32 are pending and under examination.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 23 March 2004 has been considered by the examiner. See signed and attached PTO-1449. N.B. The cited references are located in the parent application.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to crystals belonging to cytokine receptor proteins from Class I which are resistant to the addition of 10% (v/v) DMSO and 5% (v/v) DMF for at least 24 hours. The claim is rendered indefinite because the term resistant is ambiguous as to what it is pertaining to. Resistant to what? And in what way? Resistant to the crystal cracking (e.g. a serious disruption to the crystal lattice), resistant to the uptake of the DMSO and DMF through the solvent accessible channels in the crystal? The specification is of no help in understanding the term and claim either

as on p. 4, lines 5-7, the specification claim mimics the claim language without providing further detail. For this reason the claim is deemed indefinite.

5. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "maintained capacity of diffraction" is a completely subjective phrase, even with the qualifier "by using a synchrotron radiation source" for two reasons: I) and ii) the strength of the beam line and of the synchrotron radiation source (e.g. 1st generation synchrotrons compared with 3rd generation synchrotrons) will also determine the length of time a protein crystal is resistant to break down and radical damage of the crystal lattice due to the constant bombardment of the crystal with x-rays, and thus its 'maintained capacity of diffraction'. This length of time is then subsequently further 'complicated' by a proteins crystal symmetry. The time in which it takes to collect data from a particular protein crystal will vary due to a protein's crystal system and space group; for example, a protein crystal belonging to the triclinic crystal system has no crystal symmetry and will take 2-5 times more exposures to collect a complete data set as compared to a protein crystal having high crystal symmetry such as those belonging to the cubic crystal system. So the question arises of maintained capacity; for how long, and to what end? The claim ultimately is rendered indefinite because the metes and bounds of the claim remain undefined and are completely subjective.

6. Claim 30 recites the limitation "Crystals according claim 12 wherein the contact surface is between 100-900 Å^{2}" in referencing the contact surface of two molecules that are between 200-1800 Å^2 as recited in claim 12. There is insufficient antecedent basis

for this limitation in the claim (claim 30) because the lower limit of the range 100-900 does not fall within the recited range of 200-1800.

Claim Rejections - 35 USC § 112 – 1st Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement:

8. Claims 11-21 and 26-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for crystals of the human growth hormone receptor protein according to SEQ ID No: 3, does not reasonably provide enablement for any crystals of other human growth hormone receptor proteins that are modified in the extracellular domain and which are ligand free, or any other crystal of the cytokine receptor protein of the Class I cytokine family that is modified in the extracellular domain and which is ligand free. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to class I cytokine receptor crystals that have been modified in the extracellular domain and where said proteins are not complexed to a ligand molecule. However, the specification only sufficiently describes one protein crystal which falls within this genus, that being the human growth hormone receptor (hGHR) protein that has amino acids 33-234, e.g. SEQ ID No: 3 (the full length protein

is 1-237). The specification is void of any other fully described examples of hGHR proteins which have been crystallized that have been modified in the extracellular domain and that are ligand free, or any other crystals of type of class I cytokine receptor that possess the same attributes (e.g. modified in the extracellular domain and are ligand free. Thus, a skilled artisan, in order to achieve that which is claimed within the metes and bounds of the claimed invention, would be required to determine *de novo* crystallization conditions in order to make and/or use the claimed invention. In this case, the burden is seen as undue when the Wands analysis is considered.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant case, the quantity of experimentation would be considerable because the smallest change in *any* parameter in crystallizing a protein can have enormous consequences. Thus, it is not enough to have the crystallization conditions of a related/similar protein or 'native' protein. Rather, what would be required is precise instruction about how to make the protein crystal (each and every one) in order to avoid undue experimentation. In order to make the protein crystals encompassed by the scope of the claims, the following must be clear: (a) the preparation and chemical composition of the molecules to be crystallized and (b) the crystallization conditions, including methods and reagents used. Thus, new crystallization experiments must be done in order to determine if a macromolecule will crystallize, and X-ray diffraction experiments must be done in order to determine if the crystalline macromolecule is encompassed by the scope of the claims. Small changes in any of the aforementioned factors can change the unit cell dimensions and/or space group symmetry of a crystal dramatically (Giege *et al.*, 1994, noted above); therefore, precise instruction about how to make protein crystals is required so that undue experimentation is not required.

However, in the instant case, there is no direction or guidance in the specification of how a skilled artisan might achieve crystals of class I cytokine receptor proteins that are ligand free and modified in the extracellular domain (claims 11-21, 30), *or* other hHGR crystals according to SEQ ID No: 2 or 4 (claims 31-32), other than that described for the single hHGR protein crystal according to SEQ ID No: 3 (Example 1). The nature

of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a mutant or a protein complex even though they may contain a common protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein complex) (see Weber, Overview of Crystallization Methods. Methods in Enzymology, 1997, Vol. 276, pp. 13-22), and which is described for SEQ ID No: 2 in Example 1 of the instant specification. *At best*, the art of crystallization is unpredictable even to those highly skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee of success and it is even a well known fact in the art that luck often times play a fortuitous role in obtaining successful crystallization conditions despite the extremely high skill level of those in the art (see Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th paragraph, lines 1-2). Furthermore, the prior art is of little assistance because there are few examples of cytokine receptor proteins that are modified in the extracellular domain which are ligand free, and there certainly are no examples of HGR protein crystals with the same attributes, from human or any other species. Thus, the high level of unpredictability, particularly in light of the additional requirements of the crystals (unit cell, space group, etc.), which cannot be determined until after crystallization is completed, in combination

with the quantity of experimentation and the state of the prior art render the instant claims not enabled to the full extent of their scope.

Written Description:

9. Claims 11-21 and 26-32 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a genus of class I cytokine receptor crystals that have been modified in the extracellular domain and where said proteins are not complexed to a ligand molecule (Claim 1) with optional additional limitations presented in individual, dependent claim form such as: having a particular sequence (or genus of sequences) (Claims 31-32), certain crystal solvent content (Claims 13-14), certain molecular contact distances (Claims 12 and 30), or certain resolution (Claims 15-16), etc. While the structure and function of a single species of said genera of class I cytokine receptor protein crystals are disclosed in the specification, the common structural characteristics of the species that define the entire genera are not described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

To fully describe a genus of genetic material, which is a chemical compound, applicants must: (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

However, because the nature of the art of crystallization is so unpredictable, the full disclosure of even several species within a genus does not necessarily define an entire genus and allow a skilled artisan to be able to predict the successful crystallization conditions of similar proteins. In the instant case, the specification fully describes a single specie of class I cytokine receptor crystals, according to claim 1, that fall within the instant genera of crystals. Example 1, describes the crystallization of the human growth hormone receptor protein that has the N-terminus and C-terminus modified (e.g. deleted from residues 1-31 and 235-237), and where the crystal is also ligand free. The single crystal formed falls within the genera of the claims. However, it is the only species which is described.

While the claim language requires a function for the instant genera of crystals (that of class I cytokine receptors), the claims do not require, and the specification does not describe, any common characteristics that define the structure of the instant genera as a whole. In general, for a species of crystal to be adequately structurally described

in a claim, the following must be adequately disclosed: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein (preferably a SEQ ID NO of all included residues) and any molecule bound to it), (2) the space group, and (3) the unit cell dimensions of the crystal. The single specie noted above has adequately met this burden in the specification. However, the composition of the crystals encompassed by the breadth of the claims is not described, nor are the space group and unit cell dimensions associated with this breadth of chemical composition described. It is well known that a singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can *only* be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). Based on the instant the specification, the chemical composition, space group, and unit cell dimensions encompassed by the breadth of the claims is unpredictable to one of skill in the art. One of skill in the art would be unable to predict the structure of other members of the genera by virtue of the instant disclosure. Therefore, claims drawn to the instant genera of class I cytokine receptor protein crystals that are modified in the extracellular domain and which are ligand free are also not adequately described.

10. Claims 26-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of obtaining improved cytokine receptor crystals of cytokine class I receptor proteins by performing four steps: I) solving the three-dimensional structure of cytokine class I receptor proteins that are complexed to a ligand, ii) identifying at least one terminus within the three-dimensional structure that is disordered within the electron density map and likely contributes to the inhibition of non-ligated receptor crystal growth, iii) producing modified receptor proteins that have the disordered amino acids removed which were identified in step ii and iv) crystallizing the truncated receptor protein without a ligand. However, nowhere in the specification are steps i-ii) even addressed or described. Thus a skilled artisan would be required to first determine *de novo* crystallization conditions for the receptor protein and ligand, then solve the structure, assuming crystal conditions could even be found; and the requisite work involved in this process is wholly dependent upon whether the structure solution can be performed by molecular replacement or if it has to be performed *de novo* by isomorphous replacement methods (SIR or MIR) or multiple-anomalous dispersion (MAD). The Applicants have failed to meet the written description requirements because the MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.

> 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

In the instant case Applicants have failed to describe all of the method steps claimed in steps i-ii); namely the crystallization of even a single receptor protein that is ligated to a ligand and the subsequent identification of the disordered termini. Accordingly, it is deemed that the specification fails to provide adequate written description for the claimed method as it does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.30am to 4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SMN
02 March 2006

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER